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BINGHAM MCCUTCHEN LLP			RAO, SAVITHA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/589,751	<b>Applicant(s)</b> GIANCARLO ET AL.
	<b>Examiner</b> SAVITHA RAO	<b>Art Unit</b> 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 12 February 2010.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 28-43 and 47-57 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 28-43 and 47-57 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/1449)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

Claims 28-43 and 47-57 are pending .

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 02/12/2010 is acknowledged. Claim28 is amended. The claims 26-43 and 47-57 are under consideration in the instant office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/09/2010 has been entered.

Applicants' arguments, filed 02/12/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 28 and dependent claims 29-43 and 47-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is vague and indefinite in that the metes and bounds of the term "diastereoisomeric excess" is unclear. The term "diastereoisomeric excess" is unclear due to a lack of what comparison is performed to define what is meant by said "excess". Instant claims recite these terms "excess" without any indication as to an excess compared to what. This is a relative "excess" limitation in the claim and does not set forth what these terms are compared to. The term "diastereoisomeric excess" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 29-38 are rejected under 35 U.S.C. 112, second paragraph due to the unclarity of preparatory methods therein which do not clearly result in preparation of the claimed product. For e.g. instant claim 29 contains the preparation methodology of a "sterile" solution which is not what the first line of the instant claim 29 or 28 from which it depends cites as the claimed product. Also, claim 29 contains preparation methodology resulting in a vailed inert gas product which is not the solution as cited in line 1 of claim 29, but results in a sterile solution in a vial or ampoule under an inert gas atmosphere. These results in the actual metes and bounds of the subject matter of claim 29 being unclear as to whether it is the solution of line 1 therein or the result of the process of preparation methodology. For the purposes of the instant action, the solution claimed in

Art Unit: 1614

instant claim 29 and dependent claims 30-38 are being interpreted as being drawn to the solutions as recited in the first line of the instant claim 29.

***Claim Rejections - 35 USC § 112 and - 35 USC § 101***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 42 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 42 and 54 are product claims which require an action step given as "is filled....." which is not worded in claims 42 and 54 within a process of making which is different from steps recited in claim 29.

Claims 42 and 54 are rejected under 35 U.S.C. 101 because the claims recite an action step under the claim drawn towards a product. This result in an improper definition of a product, i.e., results in a claim which is not a proper product or process claim and is nonstatutory under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 103***

**New grounds of rejection necessitated by the newly submitted claims filed on  
02/12/2010**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 28-43 and 47-57 are rejected under 35 U.S.C. 35 U.S.C. 103(a) as being unpatentable, under over Buchs et al. (US 5814635, reference already of record) in view of Mueller et al. (US 6160116).

It is respectfully pointed out that claims 29-38 are product-by-process claims. As per MPEP section 2113 (R-1) product by process claims, even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or

Art Unit: 1614

obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113. Thus, because Buchs et al. teaches a product that is identical to what is instantly claimed, then the process limitations, while considered, are not patentably *limiting* to the claims because the prior art teaches an identical product and, therefore, the manner in which it was made fails to apparently result in a product different from that which is already known in the prior art.

Buchs et al. teaches a concentrated stable solution, especially an injection solution characterized in that it contains besides water either sodium-leucovorin or potassium-leucovorin or sodium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid or potassium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid (col.2, lines 15-19). Buchs et al. teaches that N(5)-Formyl-5,6,7,8-tetrahydrofolic acid, also named folinic acid, is used in the form of its calcium salt (calcium-leucovorin USP) as an agent in the cancer chemotherapy (col.1, lines 9-11). Buchs et al. teaches the method of preparation of the concentrated stable solution especially an injection solution where in Folinic acid or N (5)-methyl-5, 6, 7, 8-tetrahydrofolic acid is suspended in degassed water at room temperature under an inert gas atmosphere. The water is acceptable for the preparation of injection solutions. An aqueous solution of sodium- or potassium-hydroxide, -hydrogen carbonate or -carbonate is added in portions for a sufficient time until a clear solution is formed, which has the desired pH-value. The obtained solution is subjected to sterile filtration, and vials are filled with the resulting sterile solution under an inert gas atmosphere (col. 2, lines 20-32, patented claim 11).

Buchs et al. teaches that the preferred embodiments of his invention comprised more preferably from 2-6% weight of sodium-leucovorin or potassium-leucovorin or sodium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid or potassium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid (col.2, lines 33-39, patented claims 4- 5 and 13-15). Buchs et al. also teaches that the pH-value of the solution is more preferably 8.0 (col.2, line 40-41, patented claims 6-8 and 16) Buchs et al. additionally teaches that his invention also provides a concentrated, stable solution of the bases of folates, which contains neither a stabilizer nor complexing agents (col.2, lines 9-11). Note: It is a position of the examiner that the use of term "completing" in col.2, line 11 is a typo and is actually referring to the "complexing" agent, since the reference discloses that EDTA and similar complexing agents are not acceptable in an injection solution and it is the object of the invention to overcome that drawback in the prior art. Additionally the example of the preparation of the inventive solution does not include any stabilizing and complexing agent (page 2, line 65 to page 3, line 17). Buchs et al. additionally teaches in example the preparation of inventive solution which comprises the following steps, 200.7 g of folic acid with a water content of 10.2% by weight were suspended under stirring at room temperature in 2.5 liters of degassed, sterile water under a nitrogen atmosphere. Then was added drop by drop under stirring a 10% aqueous sodium hydroxide solution until a clear solution has been formed, which had a pH-value of 8.0. The obtained clear solution was diluted to a volume of 3.6 liters by the addition of degassed, sterile water. This diluted solution was subjected to a sterile filtration (pore size: 0.2 micrometer). The obtained sterile filtrate was filled under a nitrogen atmosphere in vials. The vials were

Art Unit: 1614

stored in a refrigerator at a temperature of 4.degree. C (page 2, line 65 to page 3, line 17). Buchs et al. also teaches that the solution of his invention can be used in the preparation of a medicament for rescues/rescue agents after treatments with high doses of methotrexate or combined with 5-fluorouracil or used in the preparation of a medicament for the treatment of megaloblastic anemia and dihydropteridin reductase deficiency (col. 2, lines 56-62 and patented claims 17-20).

Buchs et al. does not teach their inventive concentrated folinate solution to comprise a diastereoisomeric excess of the (6S) sodium-folinate or potassium folinate.

However, Mueller et al. teaches the preparation methods to synthesize sodium (6S) folinate and potassium (6S) folinate (abstract). Mueller et al. teaches that synthetic folinic acid consists of a 1:1 mixture of the two diastereomers R and S (col. 1, lines 29-31) where as in the natural state, for example in the liver folinic acid is found only in the S form and further teaches that the inverse ( R) form is barely metabolized and is slowly eliminated through the urine and is biologically inactive (col.1, lines 35-49). Mueller et al. teaches the preparation of sodium (6S) folinate by a method using calcium (6S) folinate using a cation exchanger resin (example 4, col.5) and potassium folinate by dissolving (6S) folinic acid in aqueous potassium hydroxide (example 5, col.6), Mueller et al. teaches that the (6S) sodium and potassium folinate has comparatively good water solubility and high tolerance and is therefore appropriate starting material for preparation of injectable solutions (col.3, lines 34-42) .

Accordingly, the injection solution of sodium and potassium folinate as taught by Buchs et al. in view of the teachings of Mueller et al. renders the instantly claimed

Art Unit: 1614

invention prima facia obvious. Buchs et al. expressly teaches concentrated injectable solution comprising sodium or potassium folinate. Mueller teaches that the R form of folinate is not active and provides a method of preparing pure sodium (6S) folinate. It would have been obvious to a person of ordinarily skill in the art to utilize the purified (6S) sodium folinate taught by Mueller et al. in the concentrated solution of Buchs et al. A person of ordinary skill would have been motivated to do such a substitution from the prior art knowledge that the S version of folinate is the active form and the R version is inactive and the substitution will yield solution which therefore would have better activity and bioavailability. As such a person of ordinary skill in art would be imbued with a reasonable expectation of success in developing a concentrated injectable solution with just the 6(S) form of sodium folinate instead of the racemic form as the concentrated injectable solution with the racemic form is taught in the prior art and the procedure for the preparation of the 6(S) form of sodium folinate is known in the prior art and all that is required is the simple substitution of the racemic form with the active 6(S) form of sodium or potassium folinate.

In addition, It has been determined that pure optical isomer is unpatentable over racemic mixture unless it possess unexpected properties not possessed by racemic mixture. *In re Anthony*, 414, F.2<sup>nd</sup> 1383, 162 USPQ 594 and that in absence of unobviousness, one cannot patent optical isomer over racemate, *Brever v. Ladd*, 147 USPQ 87. In addition it has been determined that in order to patent an optical isomer, it is necessary to show that they posses "qualities [which] are utterly unobtainable" in the racemic mixture. *Sterling Drug v. Watson*, 108 USPQ 37. Note also *Pfizer v. Int.*

Art Unit: 1614

*Rectifier Corp.*, 190 USPQ 273, 280; *Lilly v. Generex*, 174 USPQ 65. Accordingly, absence evidence to the contrary, the instantly claimed concentrated injection solution of sodium and potassium folinate would possess properties similar to the concentrated solution of sodium and potassium folinate for injection taught by Buchs et al. would possess similar properties and elicit actions identical to the instant. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph)

It is also noted that the expectation with regard to enantiomers is that activities as they pertain to living systems are expected to be different, *In re Adamson*, 275 F.2<sup>nd</sup> 952, 125 U.S.P.Q. 233 (C.C.P.A 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving enantiomers having substantially different pharmacological activity. It appears as though applicant has determined experimentally what a person of ordinary skill in the art would have expected, namely, that the racemic mixture of the prior art may be different (+) and (-) enantiomers possessing substantially different pharmacological activity. This is an expected result. It is well established that expected beneficial results are evidence of

obviousness of the claimed invention just as unexpected beneficial results are evidence of unobviousness, *In re Skoll*, 523, F.2<sup>nd</sup> 1392, 186 U.S.P.Q. 481 (C.C.P.A. 1975).

### ***Conclusion***

Claims 28-43 and 47-57 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/  
Examiner, Art Unit 1614

Application/Control Number: 10/589,751

Art Unit: 1614

Page 12

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